A Rationally Designed, General Strategy for Membrane Orientation of Photoinduced Electron Transfer-Based Voltage-Sensitive Dyes.

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Public Summary:
Voltage imaging with fluorescent dyes offers promise for interrogating the complex roles of membrane potential in coordinating the activity of neurons in the brain. Yet, low sensitivity often limits the broad applicability of optical voltage indicators. In this paper, we use molecular dynamics (MD) simulations to guide the design of new, ultrasensitive fluorescent voltage indicators that use photoinduced electron transfer (PeT) as a voltage-sensing switch. MD simulations predict an approximately 16% increase in voltage sensitivity resulting purely from improved alignment of dye with the membrane. We confirm this theoretical finding by synthesizing 9 new voltage-sensitive (VoltageFluor, or VF) dyes and establishing that all of them display the expected improvement of approximately 19%. This synergistic outworking of theory and experiment enabled computational and theoretical estimation of VF dye orientation in lipid bilayers and has yielded the most sensitive PeT-based VF dye to date. We use this new voltage indicator to monitor voltage spikes in neurons from rat hippocampus and human pluripotent-stem-cell-derived dopaminergic neurons.

Scientific Abstract:
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